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Impact of COVID-19 quarantines on clozapine-induced constipation: Experience of utilizing a clozapine-induced constipation protocol at a state forensic psychiatric facility

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Abstract

Objective: Since 2017, Fulton State Hospital (FSH) has implemented a clozapine-induced constipation protocol. In March 2020, FSH initiated unit quarantines to minimize the spread of coronavirus disease (COVID-19). The objective of this study was to evaluate the impact of these quarantines on medical referrals for constipation, the Bristol Stool Chart ratings, utilization of as-needed (PRN) laxatives, and adherence rates with scheduled constipation medication regimens.

Methods: Patients on the clozapine-induced constipation protocol from May 1, 2019 to December 31, 2020, were included, with 10-month pre- and mid-quarantine implementation. Data collected included patient demographics, primary psychiatric diagnosis, and outcome variables. Descriptive statistics and paired t-tests were performed.

Results: A total of 31 patients were included. Most were male (93.5%), with a median age of 40 years. The most common primary diagnosis was schizophrenia. Compared with the pre-quarantine implementation period, there were fewer medical referral contacts per person, less use of PRN laxatives, and slightly lower adherence rates to scheduled constipation medication regimens during the mid-quarantine implementation period.

Conclusion: Compared with the pre-quarantine implementation period, there were fewer medical referrals per person during the mid-quarantine implementation period.

Keywords: clozapine, constipation, schizophrenia, COVID-19, quarantine, protocol, Bristol Stool Chart

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Introduction

Clozapine is a second-generation antipsychotic and the only medication FDA-approved for treatment-resistant schizophrenia.[1–3] According to a meta-analysis on the comparative efficacy of first- or second-line treatments in schizophrenia, clozapine may exhibit superior efficacy compared to other antipsychotics.[4] Despite its efficacy, clozapine continues to be underutilized, mainly due to the risk of life-threatening adverse effects including severe neutropenia, seizures,

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myocarditis, and severe constipation.[2,3] Clozapine-related constipation is dependent on serum concentration, affecting 15% to 60% of individuals undergoing clozapine treatment, establishing it as one of the most commonly reported adverse effects.[5,6] A meta-analysis of 32 studies reported a pooled prevalence of 31.2% for clozapine-related constipation.[6] In addition, clozapine-related constipation can potentially lead to paralytic ileus and bowel obstruction, and thus be life-threatening.[7–12] It has been postulated that the anticholinergic properties of clozapine play a role in causing constipation.[5] In addition to anticholinergic properties, other factors may influence constipation, and patient self-report has low sensitivity in this context.[5] Therefore, instead of relying on patient self-reporting, a clozapine-induced constipation protocol is necessary.

Fulton State Hospital (FSH) is a 449-bed forensic psychiatric facility.[13] Since 2017, a clozapine-induced constipation protocol has been implemented to improve the detection and treatment of clozapine-induced constipation (Appendix). The protocol emphasizes both proactive bowel management and close monitoring. Abdominal imaging is performed before starting clozapine treatment. A weekly report containing an updated list of patients on clozapine, organized by unit, is emailed to all unit clerks. Clerks print the weekly reports and place them with the flow sheets to identify patients who require monitoring. All patients on the protocol are required to have their bowel movements visualized daily by staff, who proceed to assign an appropriate Bristol Stool Chart (BSC) classification. Only 1 BSC is recorded per patient per day. The BSC is a tool to classify stools into 7 types based on appearance, ranging from very hard to watery, which is useful in identifying constipation and other bowel disorders.[14] If there is no visualized bowel movement for 3 days, or a stool is visualized and reported as a BSC Type 1 or Type 7, patients are diagnosed with constipation or diarrhea and referred to an onsite medical clinic for an assessment. Approximately 1500 badge-size copies of the BSC were made for employees to wear on their badges to assist with the documentation process. All staff involved in direct patient care received the badge-size copies. All visualizations, types, referrals, medication adherence, and as-needed (PRN) medications are recorded in the hospital's Electronic Medication Administration Record. PRN laxatives are not automatically ordered when clozapine is initiated, but may be ordered at the discretion of the provider at any time during the clozapine therapy.

A new coronavirus identified in December 2019 would later become known as COVID-19.[15] This disease is transmitted by both symptomatic and asymptomatic carriers via direct contact, aerosol droplets, and the fecal-oral route.[16,17] In March 2020, the World Health Organization (WHO) declared COVID-19 a pandemic,[18] and the United States began implementing stay-at-home orders as a quarantine. Accordingly, FSH began quarantining patients to minimize the spread of COVID-19 between units. As a result of these quarantines, the number of activities offered to patients was reduced, and sedentary behavior increased. As gastrointestinal motility is associated with physical activity,[19] this study aimed to evaluate the impact of these quarantines on medical referrals for constipation, the BSC ratings, utilization of PRN laxatives, and adherence rates with scheduled constipation medication regimens.

Methods

Retrospective chart reviews were conducted for patients on the clozapine-induced constipation protocol from May 1, 2019 to December 31, 2020, were included, with a 10-month pre- and mid-quarantine implementation. Patients were excluded if they initiated clozapine after May 1, 2019, discontinued clozapine before December 31, 2020, did not participate in the clozapine-induced constipation protocol, or were transferred to another facility during the study period. All patients treated with clozapine were initially on the protocol, but the protocol might be discontinued if stool visualization resulted in aggression. The primary outcome was the number of medical referrals for constipation. This was selected as it represented the step in the protocol at which constipation was significant enough to require medical intervention. The secondary outcomes included the BSC ratings, utilization of PRN laxatives, and adherence rates with scheduled constipation medication regimens. Patients who were included served as their own control.

The BSC ratings were categorized as Types 0-7.[14] Type 0 was no bowel movement documented. Medication administration history reports were used to identify medication refusals and the utilization of PRN laxatives. Referrals made to the medical clinic for constipation were documented. Other data collected included patient demographic variables (age, gender, and race) and primary psychiatric diagnosis. Disease states were identified by the International Classification of Diseases (ICD)-9 and ICD-10 codes. Descriptive statistics and paired t-tests were performed. The study was approved by the University of Missouri-Columbia Institutional Review Board and the State of Missouri Department of Mental Health Professional Review Committee.

Results

Fifty-three patients were identified during the study period, of which 31 met the inclusion criteria. The other 22 patients were excluded because they were transferred to another facility during the study period ($n = 10$), were transferred to the facility while taking clozapine after the start of the study period ($n = 1$), started taking clozapine after the start of the study period ($n = 10$), or discontinued clozapine before the end of the study period ($n = 1$). Most patients were male (93.5%), with a median age of 40 years, and Caucasian (58%) (Table 1). The most common primary diagnosis was schizophrenia (38.7%), followed by schizoaffective disorder, bipolar type (29.1%), and schizoaffective disorder, depressive type (9.8%).

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TABLE 1: Baseline characteristics of total population ($N = 31$)

Variables	Value
Age, median years (range)	40 (24 – 65)
Sex, *n* (%)	
Male	29 (93.5)
Female	2 (6.5)
Race, *n* (%)	
Caucasian	18 (58)
African American	13 (42)
Primary diagnosis, *n* (%)	
Schizophrenia	12 (38.7)
Schizoaffective, bipolar type	9 (29.1)
Schizoaffective, depressive type	3 (9.8)
Antisocial personality disorder	1 (3.2)
Borderline personality disorder	1 (3.2)
Cyclothymic disorder	1 (3.2)
Intermittent explosive disorder	1 (3.2)
Pedophilic disorder	1 (3.2)
Sexual sadism disorder	1 (3.2)
Unspecified intracranial injury without loss of consciousness sequela	1 (3.2)

TABLE 2: Paired t-tests for instances of the Bristol Stool Chart (BSC) ratings ($N = 31$)

Stool Type	Pre-quarantine Implementation Instances of BSC Ratings per Patient, Mean (SD)	Mid-quarantine Implementation Instances of BSC Ratings per Person, Mean (SD)	*P*-Value
Type 0	186.81 (81.16)	175.32 (48.39)	.38
Type 1	1.00 (2.41)	0.90 (1.99)	.69
Type 2	2.65 (4.96)	2.45 (5.71)	.74
Type 3	8.94 (14.42)	6.23 (9.35)	.23
Type 4	68.39 (51.77)	68.39 (41.73)	1.00
Type 5	27.19 (18.57)	26.06 (21.42)	.75
Type 6	13.52 (12.93)	11.84 (12.75)	.49
Type 7	10.19 (10.42)	9.81 (10.83)	.85

The average number of medical referrals for constipation per person was 6.45 (±5.63) during the period of pre-quarantine implementation and 4.06 (±5.92) during the period of mid-quarantine implementation. The paired t-test demonstrated a statistically significant difference ($P < .05$) between the measures. The instances of BSC ratings were not statistically different between the periods of pre- and mid-quarantine implementation (Table 2). During the period of pre-quarantine implementation, milk of magnesia was utilized 589 times, magnesium citrate was utilized 17 times, lactulose was utilized 86 times, and bisacodyl was utilized once (a total of 693 times). During the period of mid-quarantine implementation, milk of magnesia was utilized 444 times, magnesium citrate was utilized 4 times, lactulose was utilized 104 times, and bisacodyl was utilized 60 times (a total of 612 times). Overall, the frequency of PRN laxative utilization was reduced by 11.6% during the mid-quarantine implementation period. Moreover, the adherence rate of scheduled constipation medication was 87% during the period of pre-quarantine implementation and 84% during the period of mid-quarantine implementation.

Discussion

The results demonstrate fewer medical referral contacts per person during the mid-quarantine implementation period. In addition, no difference in the BSC ratings was observed. The results show that the clozapine-induced constipation protocol worked well during the quarantines, even though the quarantines dramatically changed patients' daily routines and physical activity levels. The decline in PRN use indicates there was not an increased reliance on PRN laxatives by health care professionals. It was also possible that health care professionals were proactively addressing patient needs by conducting assessments and implementing treatments more quickly and informally, rather than relying solely on PRN laxatives or medical referrals. As described earlier, the protocol closely monitors patients prescribed clozapine and provides resources for managing constipation, such as medical referrals and the provision of PRN laxatives. However, it is possible that confounding factors were not fully measured. A number of factors contribute to constipation, including insufficient dietary fiber, dehydration, female gender, increasing age, socioeconomic status, educational level, physical activity, self-rated health, certain medical conditions, and certain medications.[20–22] In addition, there was a push on the wards to encourage activity and mobility, but this was not accounted for, so patients might have been physically active in the wards or their rooms. Another limitation is the small sample size ($n = 31$), located in a single practice setting, which can limit the generalizability of the results.

The clozapine-induced constipation protocol is innovative in 3 aspects. First, it takes a proactive approach to bowel management promoting early identification and treatment of constipation. Daily monitoring of bowel movements by trained staff helps detect any changes in bowel function and take appropriate measures to prevent constipation. These complications may require surgical interventions, which can be costly and have a significant impact on patient's quality of life. Second, the protocol incorporates the BSC into the process. The BSC provides a standardized model for consistent reporting of bowel function across settings and populations. Based on our experience, the BSC is easy for staff to use and for patients to understand. In addition, the BSC has demonstrated benefit in diagnosing various bowel disorders. For example, Types 1 and 2 stools are indicative of constipation, while Types 5-7 stools are associated with diarrhea.[14] Its diagnostic utility can also be used to monitor the effectiveness of a treatment. Third, the protocol engages patients and involves direct care staff, nurses, pharmacists, and physicians. It standardizes and includes medical referrals and the

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provision of PRN laxatives. It supports a multidisciplinary approach of regular bowel monitoring, medication management, dietary modification, and physical activity to address a potentially significant adverse event.

Conclusion

Compared with the pre-quarantine implementation period, there were fewer medical referrals per person during the mid-quarantine implementation period. Other factors that might impact the clozapine-induced constipation and patient self-report had low sensitivity in this context.

References

1. Stępnicki P, Kondej M, Kaczor AA. Current concepts and treatments of schizophrenia. Molecules. 2018;23(8):2087. DOI: 10.3390/molecules23082087
2. Meltzer HY. Clozapine: balancing safety with superior antipsychotic efficacy. Clin Schizophr Relat Psychoses. 2012;6(3):134-44. DOI: 10.3371/CSRP.6.3.5
3. De Berardis D, Rapini G, Olivieri L, Di Nicola D, Tomasetti C, Valchera A, et al. Safety of antipsychotics for the treatment of schizophrenia: a focus on the adverse effects of clozapine. Ther Adv Drug Saf. 2018;9(5):237-56. DOI: 10.1177/2042098618756261
4. Okhuijsen-Pfeifer C, Huijsman EAH, Hasan A, Sommer IEC, Leucht S, Kahn RS, et al. Clozapine as a first- or second-line treatment in schizophrenia: a systematic review and meta-analysis. Acta Psychiatr Scand. 2018;138(4):281-8. DOI: 10.1111/acps.12954
5. Every-Palmer S, Nowitz M, Stanley J, Grant E, Huthwaite M, Dunn H, et al. Clozapine-treated patients have marked gastrointestinal hypomotility, the probable basis of life-threatening gastrointestinal complications: a cross sectional study. EBioMedicine. 2016;5:125-34. DOI: 10.1016/j.ebiom.2016.02.020
6. Shirazi A, Stubbs B, Gomez L, Moore S, Gaughran F, Flanagan R, et al. Prevalence and Predictors of Clozapine-Associated Constipation: A Systematic Review and Meta-Analysis. IJMS. 2016;17(6):863. DOI: 10.3390/ijms17060863
7. Levin TT, Barrett J, Mendelowitz A. Death from clozapine-induced constipation: case report and literature review. Psychosomatics. 2002;43(1):71-3. DOI: 10.1176/appi.psy.43.1.71
8. Palmer SE, McLean RM, Ellis PM, Harrison-Woolrych M. Life-threatening clozapine-induced gastrointestinal hypomotility: an analysis of 102 cases. J Clin Psychiatry. 2008;69(5):759-68. PubMed PMID: 18452342
9. Hibbard KR, Propst A, Frank DE, Wyse J. Fatalities associated with clozapine-related constipation and bowel obstruction: a literature review and two case reports. Psychosomatics. 2009;50(4):416-9. DOI: 10.1176/appi.psy.50.4.416
10. Flanagan RJ, Ball RY. Gastrointestinal hypomotility: An under-recognised life-threatening adverse effect of clozapine. Forensic Sci Int. 2011;206(1-3):e31-e36. DOI: 10.1016/j.forsciint.2010.07.021
11. Nielsen J, Meyer JM. Risk factors for ileus in patients with schizophrenia. Schizophrenia Bulletin. 2012;38(3):592-8. DOI: 10.1093/schbul/sbq137
12. West S, Rowbotham D, Xiong G, Kenedi C. Clozapine induced gastrointestinal hypomotility: A potentially life threatening adverse event. A review of the literature. Gen Hosp Psychiatry. 2017;46(Suppl. 9):32-7. DOI: 10.1016/j.genhosppsych.2017.02.004
13. Missouri Department of Mental Health. About Fulton State Hospital. Available from: https://dmh.mo.gov/opla/pprp/about#
14. Lewis SJ, Heaton KW. Stool form scale as a useful guide to intestinal transit time. Scand J Gastroenterology. 1997;32(9):920-4. DOI: 10.3109/00365529709011203
15. Helmy YA, Fawzy M, Elaswad A, Sobieh A, Kenney SP, Shehata AA. The COVID-19 pandemic: a comprehensive review of raxonomy, genetics, epidemiology, diagnosis, treatment, and control. JCM. 2020;9(4):1225. DOI: 10.3390/jcm9041225
16. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-3
17. Li J-Y, You Z, Wang Q, Zhou Z-J, Qiu Y, Luo R, et al. The epidemic of 2019-novel-coronavirus (2019-nCoV) pneumonia and insights for emerging infectious diseases in the future. Microbes Infect. 2020;22(2):80-5. DOI: 10.1016/j.micinf.2020.02.002
18. WHO Director-General's opening remarks at the media briefing on COVID-19 – March 2020.
19. Kim YS. Aerobic exercise improves gastrointestinal motility in psychiatric inpatients. WJG. 2014;20(30):10577. DOI: 10.3748/wjg.v20.i30.10577
20. National Institute of Diabetes and Digestive and Kidney Diseases. Eating, diet, & nutrition for constipation. Available from: https://www.niddk.nih.gov/health-information/digestive-diseases/constipation/eating-diet-nutrition
21. Mugie SM, Benninga MA, Di Lorenzo C. Epidemiology of constipation in children and adults: a systematic review. Best Pract Res Clin Gastroenterology. 2011;25(1):3-18. DOI: 10.1016/j.bpg.2010.12.010
22. Werth BL, Christopher S-A. Potential risk factors for constipation in the community. WJG. 2021;27(21):2795-817. DOI: 10.3748/wjg.v27.i21.2795

APPENDIX: Clozapine-induced constipation protocol at FSH

Key Components

- Baseline Abdominal Imaging Studies: Before initiating clozapine treatment, all patients undergo baseline abdominal x-ray studies. Additional imaging studies are ordered as needed based on the physician's discretion.
- Bristol Stool Chart Documentation: To facilitate accurate assessment and documentation, nurses and Forensic Rehabilitation Specialists (FRS) visually classify stool types using the Bristol Stool Chart. This information is then recorded on the flow sheet. The flow sheet is a paper document that FRS and nurses keep in a book on the wards for different types of monitoring such as hygiene, stool types, vital signs, total hours slept, meals, and so on. The paper copy becomes part of the patient's medical record and is entered into the Electronic Medication Administration Record (eMAR).
- Bristol Stool Chart Badge References: Convenient badge-size copies of the Bristol Stool Chart have been distributed to all hospital employees. These charts are worn on employee badges, enabling easy access during assessments and documentation.
- Weekly Clozapine Patient Reports: An updated list of clozapine patients, categorized by ward, is compiled into a weekly report and disseminated to all ward clerks. These reports are generated through an internal clozapine database, overseen

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by the clinical pharmacist who manages the Clozapine Risk Evaluation and Mitigation Strategy (REMS) Program at FSH.

- Monitoring Guidelines for Nurses and FRS: Using the weekly reports provided by the ward clerks, nurses, and FRS are informed about which patients require monitoring.
- Stool Type Documentation in eMAR: Nurses record stool types in eMAR, accessible via computerized prescriber order entry. To prompt timely documentation, a daily reminder event in eMAR occurs at 12:00 PM. The pharmacy is responsible for entering the event that triggers nurses/direct care staff to document a patient's stool type for the day.
- Action Plan for Stool Types 1 and 7: If stool Types 1 or 7 are reported or observed, a Medical Summary Report is completed, prompting an immediate physician assessment for affected patients. When pharmacists are notified, they assist clinic providers in providing appropriate treatment and ensure communication has been provided to the patient's psychiatric provider and treatment team for ongoing monitoring.
- Management of No Bowel Movement: In cases where no bowel movement is reported or visualized for 3 days, physicians are promptly notified for a medical 1:1 and patient assessment. If necessary, close observation with 15-minute checks may be initiated at the physician's discretion, especially during employee shortages.

Pharmacists' Involvement

The development of the clozapine-induced constipation protocol was spearheaded by a clinical pharmacist, who collaborated with fellow pharmacists and an employee from Staff Development. The pharmacist presented the proposed protocol during an Intensive Case Review Committee meeting, leading to its acceptance. Subsequently, the Chief Nursing Executive (CNE) established a multidisciplinary Clozapine Work Group to facilitate the protocol's implementation and ongoing maintenance. The clinical pharmacist played a pivotal role in coordinating these efforts and assigning specific responsibilities to Clozapine Work Group members. Additionally, another pharmacist focused on implementing the necessary aspects of documentation within the Computerized Physician Order Entry (CPOE) system. Each team member had distinct responsibilities for educating and training their respective departments and disciplines, including providers, pharmacists, nursing staff, social workers, psychologists, FRS, and ward clerks. The Clozapine Review Committee, comprised of providers and pharmacists, and chaired by a pharmacist, was also consulted to provide valuable input for the successful implementation and maintenance of the protocol, combining clinical expertise with operational insight.

Before the COVID-19 pandemic, following the implementation of our protocol, the Clozapine Review Committee collaborated with providers and pharmacists to address clozapine-induced constipation issues. Every 3 months, the FSH clinic's general practitioner provided the committee with a list of patients who were regularly seen in the clinic for constipation. The pharmacists collected essential data, including stool types from the past 30 days (or since clozapine initiation if $<$30 days), Anticholinergic Risk Scale (ARS) scores, total daily clozapine doses, recent clozapine levels, scheduled and PRN constipation medications (including refusals), and relevant concomitant medications that might affect clozapine levels. The pharmacy team provided recommendations based on the essential data collected, which were discussed and finalized by the committee.

During the COVID-19 pandemic, which led to employee shortages and high turnover, a notable shift occurred in the responsibility for managing patients with clozapine-induced constipation. These unique challenges presented by COVID-19 elevated the pharmacists' involvement in patient reviews, monitoring, and addressing constipation concerns among individuals prescribed clozapine.

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